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10/728,055	12/04/2003	George Mulligan	MPI02-202PIRNM	8930
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MILLENNIUM PHARMACEUTICALS, INC. 40 Landsdowne Street CAMBRIDGE, MA 02139			EXAMINER REDDIG, PETER J	
			ART UNIT 1642	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/728,055	Applicant(s) MULLIGAN ET AL.	
	Examiner Peter J. Reddig	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 June 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4,5,7,10,29-33 and 42 is/are pending in the application.
- 4a) Of the above claim(s) 30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,5,7,10,29,31-33 and 42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/6/06 6/11/07</u> . | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. The response filed on 11 June 2007 to the restriction requirement of 8 January 2007 has been received. Applicant has elected Group I (claims 1, 2, 4, 5, 7, 10 and 29-33), drawn to a method for determining a bortezomib therapy regimen for treating a liquid tumor in a patient, wherein the level of expression of the feature in the predictive marker set is determined by detection of mRNA, wherein the feature is feature number 149, and the species A. 1), features with a rank under 100; B. 1), myelomas for liquid tumor; C. 1) prior to tumor therapy; D. 1) Signal-to-Noise Ratio method; and E. 1) Table 4 for examination. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse MPEP 818.03(a).

Applicants have added new claims 42 asserting that the new claim reads on the elected invention. This is found persuasive.

2. Claims 1, 2, 4, 5, 7, 10, 29-33 and 42 are pending.

3. Upon review and reconsideration, the "features" of Table 1 from which a predictive marker set is selected will be rejoined as the selection of features is a step in the method for which prior determination cannot appropriately be made without performing the process of feature selection as contemplated in the specification. Additionally, multiple myeloma will be rejoined with myeloma, as it is a species of myeloma.

4. Claim 30 has been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

5. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 as drawn to the species elected above are currently under consideration.

***Specification***

6. The disclosure is objected to because of the following informalities: The phrase the "table below" on p. 152, paragraph 249 should be changed to refer to Table 5 specifically, because formatting of a final patent document, if the case were to be allowed, would likely change the positions of paragraph 249 and Table 5.

Additionally, there are two periods at the end of the sentence bridging p. 16- 17.

Additionally, it appears that the word "if" should be "of" in the 2<sup>nd</sup> line of paragraph [00220].

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42, are indefinite because the term "significant expression level" in claim 1 is a relative term which renders the claim indefinite. The term "significant expression level " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What level of significant expression is required to meet the limitations of the claims? Can the features

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show underexpression or overexpression? Can some features be overexpressed and some underexpressed? Thus, the metes and bounds of the claims cannot be determined.

9. Claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42 are indefinite because all of the predictive markers in tables 1 and 4 are drawn to accession numbers, and no sequence listing data is found. The use of accession numbers does not satisfy the requirements of 35 USC 112, second paragraph because accession numbers and the sequences corresponding to accession numbers are not unique identifiers required for identification of mRNAs because accession numbers can be modified, changed, and/or updated, and thus the cited sequence may vary or change over time. Thus, identifying a molecule by accession number does not provide a reliable unique identifier. Amendment of tables 1 and 4 to include unique identifiers to sequences listed in a sequence listing which unambiguously define the molecules in the claimed Tables would obviate this rejection.

For submission of a sequence listing, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

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10. Claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42 are indefinite because it is unclear which, if any, predictive marker set, including Table 4, will indicate that a patient is responsive or non-responsive to bortezomib therapy.

11. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps in claim 1 and its dependent claims (claims 2, 4, 5, 7, 10, 29, 31-33 and 42) are: The steps required for selecting features for the set and the step of isolating a patient sample from which to determine the level of expression of features in the marker set.

12. Claims 1, 2, 4, 7, 10, 29, 31-33 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements in claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42, are: A control for comparing the expression level of the features to determine if the expression is significant or not.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for determining a bortezomib therapy regimen for treating a myeloma in a patient comprising: a) selecting features from the Predictive Markers in Table 1, to select a predictive marker set; wherein the selected predictive marker set is Table 4 b) determining the level of expression of the features in the predictive marker set of Table 4; and c) determining a bortezomib regimen for treating the tumor based on the expression of the features in the predictive marker set of Table 4, wherein a significant expression level is indicative that the patient is either a responsive patient or a non-responsive patient, wherein the expression level is determined by mRNA detection.

The predictive makers of Table 1 and Table 4 are identified by their accession number, see Tables 1 and 4.

One cannot extrapolate the teachings of the specification to the enablement of the claims because the markers in Table 1 and Table 4 are only identified by accession numbers and no sequence information is given for the markers. Accession numbers and the sequences

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corresponding to accession numbers are not unique identifiers because accession numbers can be modified, changed, and/or updated, and thus the cited sequence may vary or change over time. Thus, undue experimentation would be required for one of skill in the art to identify and use the 475 sequences in Table 1 or the 40 sequences listed in Table 4 for the method as claimed.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

14. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4)

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the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for determining a bortezomib therapy regimen for treating a myeloma in a patient comprising: a) selecting features from the Predictive Markers in Table 1, to select a predictive marker set; wherein the selected predictive marker set is Table 4 b) determining the level of expression of the features in the predictive marker set of Table 4; and c) determining a bortezomib regimen for treating the tumor based on the expression of the features in the predictive marker set of Table 4, wherein a significant expression level is indicative that the patient is either a responsive patient or a non-responsive patient, wherein the expression level is determined by mRNA detection.

The specification teaches that using the expression data from 44 multiple myeloma patients with high quality gene expression data candidate markers that correlated with the outcome of multiple myeloma patients to a proteasome inhibition (e.g., bortezomib) therapy were selected by using a combination of marker ranking algorithms. Supervised learning and feature selection algorithms were then used to identify the markers of the present invention, see para 00215 and 00216 and Table 1.

The specification teaches that a set of one or more gene transcripts that together classify samples into sensitive and resistant groups (or responsive and non-responsive), in the context of a particular classifier algorithm, is referred to as a "model." The gene transcripts are referred to as "features." Determining which combination of gene transcript(s) best classifies samples into sensitive and resistant groups is referred to as "model selection," see para. 00220.

The specification teaches that the first step in model selection is to filter the 44,928 features down to a smaller number which show a correspondence with the sample classifications. The specification teaches that filtering involves first ranking the features by a scoring method, and then taking only the highest ranking features for further analysis. The filtering algorithms used in the present invention were: (1) Signal-to-Noise Ratio ("SNR"), (2) Class-Based Threshold ("CBT"), (3) Pooled Fold Change ("PFC"), and (4) the Wilcoxon Rank-Sum Test. The specification teaches that in preferred embodiments, SNR was used to identify genes showing a small but consistent change in levels, see para 00222

The specification teaches that SNR is computed from the log expression values as absolute value of the difference in class means divided by the sum of the class standard deviations, and has been used to analyze expression data before. The specification teaches that to use SNR for filtering, the features with the top 100 SNR scores were retained and the remainder discarded from consideration, see para 00223.

The specification teaches that using the 44,928 probe sets markers were analyzed for differential expression across the 44 patient samples. In particular, we applied PFC (run 1), PFC (run 2), SNR, the Wilcoxon rank-sum test and the Class-Based Threshold. The first three methods were run in each direction, to look for genes up in responders and then up in non-responders. In each case, the probe sets were sorted based on their score, and ranked. The top 100 ranked probe sets from each method were selected for Table 1. The last column in the table identifies the minimum rank across the methods, see para 00229.

The specification teaches that feature selection is the process of determining the best subset of the 44,928 available features in the dataset, resulting in a combination of features, that

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form a marker set or model, to classify patients into sensitive and resistant groups. The first step is filtering to the top 100 markers, as described above. Next, for building Weighted Voting (WV) marker sets, a standard feature selection method, sequential forward feature selection, is used, see para 00238.

The specification teaches that for the WV models, the top 100 SNR markers were determined. Sequential forward selection starts with no markers in the set, see para 00239. The specification teaches that at each iteration, a new feature set is formed by adding a feature selected by an evaluation function. Iteration terminates when no feature can be added that improves the evaluation function. The evaluation function has two parts. The first part is the number of samples correctly predicted either (1) by the model built on all of the samples, or (2) in leave-one-out cross-validation, see para 00240.

The specification teaches that each probe set was used as a single-marker model to predict bortezomib response. Multiple marker sets were generated by repeated rounds of feature selection, each time removing the features already selected. The score of each model was determined. The probe set comprising the highest-scoring model was selected, see para 00241.

The specification teaches that the remaining probe sets were each used one at a time in a model along with the already-selected probe set(s). Each of these models was given a score. If the score of the new model was no higher than the score of the already-selected markers, then marker selection stopped, and the algorithm goes on to final selection by setting aside and continuing with selection of additional set(s) (see below). Otherwise, the probe set that was added to the already-selected markers to obtain the model with the highest score was added to

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the list of selected markers, and the algorithm returns to selection of additional markers to improve the score, see para 00242.

The specification teaches that upon final selection where no additional marker improves the score, the selected markers are set aside. Marker selection is then initiated as described above. This process is repeated until there are 5 sets of selected markers. These are combined into one complete predictive marker set, see para 00243.

The specification teaches that an example of a weighted voting predictive marker set identified using the WV and SNR scored markers is set forth in Table 4. This procedure is one of many described herein as well as others known in the art, which can be used to identify and select markers for sets predicting proteasome inhibition response in cancer patients, see para 00245.

The specification teaches an example of how to apply a Weighted Voting model to obtain a prediction of Response or Non-response for a given patient, using the algorithm described in the specification. Using the 44 patients classified into Responsive or Nonresponsive groups, the table below shows the SNR scores and decision boundaries for each of the markers in a Weighted Voting predictive set built from the data set. Also indicated is whether the marker is more highly expressed in Responsive (R) or in Non-responsive (NR) patients. For one illustrative Non-responsive patient in the data set, the votes contributed by each marker are shown in Table 5. The sum of the vote weights is less than 0, indicating a prediction of Non-responsive. The confidence in the predicted class (Non-responsive) is 0.8431, see para 00249.

One of skill in the art cannot extrapolate the teachings of the specification to the enablement of the claims because **NO** nexus has been established between determining the level

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of expression of the features in the predictive marker set of Table 4 and determining a bortezomib regimen for treating myeloma and because those of ordinary skill in the art recognize that identification of prognostic markers is unpredictable.

In particular, Mulligan et al. (Blood, 2007, 109:3177-3188, IDS) teach that although they identified a pretreatment pattern of pretreatment gene expression pattern and predictive classifier that is significantly associated with subsequent myeloma response to bortezomib but not dexamethasone, the predictive accuracy required of a clinical diagnostic for myeloma treatment has not yet been defined, see p. 3186, 4<sup>th</sup> full para. and last para. Furthermore, Mulligan et al. teach that the “Requirements may vary according to disease stage, therapeutic options, (single agent versus combination regimen) and whether therapy is likely to achieve disease control or cure. Although the classifier described here is promising, further refinement is necessary before it can be considered for clinical use in predicting patient response to single-agent bortezomib in the relapsed setting . . . Additional research is needed to assess the relevance of these genomic predictors in newly diagnosed myeloma . . . ” see p. 3186, last para. Given the above and given that the predictive marker set of Table 4 is not the marker set for myeloma identified by Mulligan et al., in the absence of additional, undue experimentation, one of skill in the art could not determine a bortezomib regimen for treating myeloma based on the level of expression of the features in the predictive marker set of Table 4.

Furthermore, although drawn to prognostic markers for early lung cancer detection, the basic principles taught are clearly applicable to determining a bortezomib regimen for treating myeloma based on the level of expression of the features in the predictive marker set of Table 4. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a

prognostic biomarker to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early markers of carcinogenesis that have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known cancer outcome. The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between marker and subsequent acknowledged disease is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of determining a bortezomib regimen for treating myeloma based on the level of expression of the features in the predictive marker set of Table 4, the predictive marker set must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

Applicant is reminded that MPEP 2164.03 teaches “the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention,

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and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

15. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations."

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(Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for determining a bortezomib therapy regimen for treating a myeloma in a patient comprising: a) selecting features from the Predictive Markers in Table 1, to select a predictive marker set; wherein the selected predictive marker set is Table 4 b) determining the level of expression of the features in the predictive marker set of Table 4; and c) determining a bortezomib regimen for treating the tumor based on the expression of the features in the predictive marker set of Table 4, wherein a significant expression level is indicative that the patient is either a responsive patient or a non-responsive patient, wherein the expression level is determined by mRNA detection.

The specification teaches as set forth above and the specification teaches that an example of a weighted voting predictive marker set identified using the WV and SNR scored markers is set forth in Table 4.

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between any expression level of the markers in Table 4 and any indication that a patient is responsive or non-responsive to bortezomib therapy. The specification has not taught the use of the marker set of table 4 for determining a bortezomib therapy regimen for any patient. There is no teaching as to what levels of expression of the markers in Table 4 will be significant for indicating responsiveness or nonresponsiveness. There

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is no teaching as to whether the marker set of Table 4 can be used for indicating responsiveness, non-responsiveness, or both. There is no teaching if just some or all of the markers in Table 4 are needed to determine a bortezomib therapy regimen. Thus, given the above, undue experimentation would be required for one of skill in the art to make and use the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches “the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above

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reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. Claims 1, 2, 4, 5, 7, 10, 29, 31-32 and 42 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

The claims are broadly drawn to a method for determining a bortezomib therapy regimen for treating a myeloma in a patient comprising: a) selecting features from the Predictive Markers in Table 1, to select a predictive marker set; b) determining the level of expression of the features in the predictive marker set; and c) determining a bortezomib regimen for treating the tumor based on the expression of the features in the predictive marker set, wherein a significant expression level is indicative that the patient is either a responsive patient or a non-responsive patient, wherein the expression level is determined by mRNA detection.

The state of the art is such that it is well known in the art that identification of biomarkers is unpredictable. In particular, Mulligan et al. (Blood, 2007. 109:3177-3188, IDS) teach that although they identified a pretreatment pattern of pretreatment gene expression pattern and predictive classifier that is significantly associated with subsequent myeloma response to bortezomib but not dexamethasone, the predictive accuracy required of a clinical diagnostic for myeloma treatment has not yet been defined, see p. 3186, 4<sup>th</sup> full para. and last para.

Furthermore, Mulligan et al. teach that the "Requirements may vary according to disease stage, therapeutic options, (single agent versus combination regimen) and whether therapy is likely to achieve disease control or cure. Although the classifier described here is promising, further refinement is necessary before it can be considered for clinical use in predicting patient response to single-agent bortezomib in the relapsed setting . . . Additional research is needed to

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assess the relevance of these genomic predictors in newly diagnosed myeloma . . . ” see p. 3186, last para. Furthermore, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a prognostic biomarker to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early markers of carcinogenesis that have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known cancer outcome. The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between marker and subsequent acknowledged disease is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points).

Given the above and given that Table 1 has 171 features with a signal to noise ratio method rank of under 100 from which to chose to select a predictive marker set, which is approximately  $1.2 \times 10^{309}$  combinations by factorial analysis (that is  $171! = 7.5 \times 10^{309}$ ), However, the specification provides no written description of which set will in fact function as claimed. An adequate written description of the predictive marker set that is useful for determining a bortezomib therapy regimen is required for one of skill in the art to use the claimed invention.

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Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Id.* At 1567, 43 USPQ2d at 1405. The court also stated that

a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

*Id.* At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Id.*

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." *Id.*

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The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a predictive marker set that is useful for determining a bortezomib therapy regimen, per Lilly by structurally describing a representative number of predictive marker sets that are useful for determining a bortezomib therapy regimen, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a predictive marker set that will function as claimed, that is useful for determining a bortezomib therapy regimen, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any predictive marker set that is useful for determining a bortezomib therapy regimen, nor does the specification provide any partial structure of such a predictive marker set that is useful for determining a bortezomib therapy regimen, nor any physical or chemical characteristics of a predictive marker set that is useful for determining a bortezomib therapy regimen, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses Table 4, 5, and 6, there is no teaching that these sets will in fact function as claimed and even if they were to function as claimed, this does not provide a description of a predictive marker set that is useful for determining a bortezomib therapy regimen that would satisfy the standard set out in Enzo especially given that the number of sets claimed exceeds the numbers of stars in the known universe.

The specification also fails to describe a predictive marker set that is useful for determining a bortezomib therapy regimen by the test set out in Lilly. The specification describes only Tables 4, 5, and 6, but there is no teaching that these sets will in fact function as claimed and even if they were to function as claimed, given that the number of sets claimed exceeds the numbers of stars in the known universe, the sets described in the three tables do not meet the test set out in Lilly. Therefore, it necessarily fails to describe a "representative number" of a predictive marker set that is useful for determining a bortezomib therapy regimen. In

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addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a broadly claimed predictive marker set that is useful for determining a bortezomib therapy regimen that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention. Since the specification fails to adequately describe or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed predictive marker set that is useful for determining a bortezomib therapy regimen, it also fails to adequately describe the claimed method or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

17. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The combination of steps a, b and c in claim 1, as amended on 10/26/2006, for determining a bortezomib regimen for treating a liquid tumor in a patient claimed in claim 1 has no clear support in the specification and the claims as originally filed. In the remarks of October 26, 2006 Applicant pointed to support for the amendment to claim 1 in the specification in paragraphs [0018], [0056], [0050], [0061] and [00220]. A review of the specification discloses support for constructing marker sets from the individual predictive markers set forth in Table 1 Table 2 and Table 3 [0018]; a description of the markers in Table 1 [0050]; determining the expression of at least one, two or more of the identified predictive markers; or three or more of the identified

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predictive markers comprising a set of the identified predictive markers and assessing the expression of a set or panel of predictive markers, *i.e.*, the expression profile of a predictive marker set [0056]; a method for determining whether an proteasome inhibition therapeutic regimen (e.g., a proteasome inhibitor agent (e.g., bortezomib) alone or in combination with another chemotherapeutic agent) can be used to reduce the growth rate of a tumor comprising the steps of: (a) determining the expression profile of a predictive marker or predictive marker set; and (b) identifying that a proteasome inhibition therapeutic agent is or is not appropriate to reduce the growth rate of the myeloma cells based on the expression profile, [0061]; a set of one or more gene transcripts that together classify samples into sensitive and resistant groups (or responsive and non-responsive), in the context of a particular classifier algorithm, is referred to as a "model." The gene transcripts are referred to as "features." Determining which combination of gene transcript(s) best classifies samples into sensitive and resistant groups is referred to as "model selection," [00220]. The suggested support is not found persuasive because there is nothing in the specification to suggest the specific combination of steps for determining a bortezomib therapy regimen for treating a liquid tumor in a patient. Thus, the subject matter claimed in claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 broadens the scope of the invention as originally disclosed in the specification.

18. Claim 42 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "a predictive marker set comprises Predictive Marker No. 149" claimed in claim 42 has no clear support in the specification and the claims as originally filed. A review of the specification and claims as originally filed has not identified support for the newly filed claim and Applicant has not

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specifically pointed to support for this newly filed claim. The subject matter claimed in claim 42 broadens the scope of the invention as originally disclosed in the specification.

19. No claims allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on (571) 272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Peter J. Reddig  
Examiner  
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**SUSAN UNGAR, PH.D**  
**PRIMARY EXAMINER**  


PJR